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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/633,698	08/05/2003	Conrad Padraig Quinn	1581.0770001	5476

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EXAMINER	
KAM, CHIH MIN	
ART UNIT	**PAPER NUMBER**
1656	

DATE MAILED: 10/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/633,698	QUINN ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☒ Claim(s) *1-21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 August 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/763,669.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1-21 are pending.

Applicants' amendments and response filed July 27, 2005 is acknowledged. Applicants' response has been fully considered. Claim 5 has been amended, and claims 22-54 have been cancelled. Therefore, claims 1-21 are examined.

Withdrawn-Claim Objection

2. The previous objection to claims 5, 12 and 19 is withdrawn in view of applicants' amendment to the claim in the amendment filed July 27, 2005.

Withdrawn Claim Rejections-Obviousness Type Double Patenting

3. The previous rejection of claims 1-4, 6-11, 13-18, 20 and 21 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 9 and 14 of U. S. Patent 6,632,440, is withdrawn in view of applicant's terminal disclaimer filed July 27, 2005, and applicant's response at page 9 in the amendment filed July 27, 2005.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating hypersecretion of mucus, asthma and COPD, the method comprising administering topically to the airways of a patient in need thereof, a compound comprising a light chain (L-chain) or L-chain fragment of a clostridial neurotoxin

containing the active proteolytic enzyme domain, a targeting domain that binds to a target cell of a mucus secreting cell or a neuronal cell controlling or directing mucus secretion, and a translocating domain that translocates the L-chain or L-chain fragment into the target cell, wherein the translocating domain is a translocating domain of clostridial neurotoxin, with the proviso that the compound is not a botulinum toxin, does not reasonably provide enablement for a method of treating hypersecretion of mucus, asthma and COPD, administering topically to the airways of a patient in need thereof, a compound comprising a light chain (L-chain) or L-chain fragment of a clostridial neurotoxin containing the active proteolytic enzyme domain, a targeting domain that binds to a target cell of a mucus secreting cell or a neuronal cell controlling or directing mucus secretion, and a translocating domain that translocates the L-chain or L-chain fragment into the target cell, with the proviso that the compound is not a botulinum toxin, wherein the translocating domain is not identified or defined. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-21 encompass a method of treating hypersecretion of mucus, asthma and COPD by administering to a patient in need thereof, a compound comprising a light chain (L-chain) or L-chain fragment of a clostridial neurotoxin, a targeting domain that binds to a target cell of a mucus secreting cell or a neuronal cell controlling or directing mucus secretion, and a translocating domain, with the proviso that the compound is not a botulinum toxin. The specification, however, only discloses cursory conclusions (pages 2-3) without data supporting the findings, which state that a compound comprising an inhibiting domain comprising a light chain of a clostridial neurotoxin or a active fragment or variant thereof, a translocating domain

that translocates the inhibiting domain into the cell, and a targeting domain that binds to a target cell of a mucus secreting cell or a neuronal cell controlling or directing mucus secretion, can be used to treat hypersecretion of mucus, asthma and COPD. There are no indicia that the present application enables the full scope in view of the use of a compound comprising the inhibiting domain, the targeting domain and the translocating domain in treating hypersecretion of mucus, asthma and COPD as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance as to how the full scope of the claims is encompassed. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the absence or presence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified amounts of variants regarding the translocating domains in the compounds which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

The specification describes the preparation of substance P-LH_N/A conjugate (Example 1); the preparation of a broad specificity agent WGA-LH_N/A (Example 2; WGA= wheat germ agglutinin); the use of WGA-LH_N/A in inhibiting neurotransmitter release from cultured neuronal cells (Example 3); a method for preparation of LC/B-$DT_{194-380}$-EGF (DT= diphtheria

toxin; Example 4), LC/B-$PE_{405-613}$-EGF (PE= pseudomonas exotoxin; Example 5), or LC/A-HA-EGF (HA= influenza virus haemagglutinin; Example 6). The specification demonstrates the inhibition of neurotransmitter release by WGA-LH_N/A in vitro (Example 3), however, there are no working examples indicating the claimed methods in association with the variants.

(3). The state of the prior art and relative skill of those in the art:

The related art (e.g., Shone *et al.*, WO 98/07864) teaches a polypeptide which has the first domain and second domains obtained from a clostridial toxin, can be translocated into the target cell and cleave the plasma-membrane associated proteins essential to exocytosis due to the functions of two domains, and the polypeptide can also contain a third domain (e.g., the Hc domain of the native toxin could be replaced by a targeting domain) that targets to a specific cell, thus the polypeptide is useful in inhibition of exocytosis in target cell such as the neuronal cell; Aoki *et al.* (WO 95/17904) teach botulinum toxins are used to treat cholinergic controlled secretions such as excessive mucus secretion; and Sanders *et al.* (WO 95/28171) teach botulinum toxin is used to treat autonomic nerve dysfunction such as asthma and COPD. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the use of the compounds containing various translocating domains in the treatment of hypersecretion of mucus, asthma and COPD to be considered enabling for variants.

(4). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method of treating hypersecretion of mucus, asthma and COPD, comprising administering topically to the airways of a patient in need thereof, a

compound comprising a light chain (L-chain) or L-chain fragment of a clostridial neurotoxin, a targeting domain that binds to a target cell, and a translocating domain that translocates the L-chain or L-chain fragment. The specification has demonstrated the inhibition of neurotransmitter release from cultured neuronal cells by WGA-LH_N/A (Example 3), it has not demonstrated the use of compounds containing various translocating domains in treating hypersecretion of mucus, COPD and asthma, and there are no working examples indicating the claimed methods associated with variants. Furthermore, the specification has not shown the effects of the compounds containing various translocating domains in the treatment. Since the specification fails to provide sufficient guidance on the use of the compounds containing various translocating domains in the treatment, it is necessary to have additional guidance and to carry out undue experimentation to use the compound in the treatment.

(5). Predictability or unpredictability of the art:

The claims encompass a method of treating hypersecretion of mucus, COPD and asthma using the compounds comprising a light chain (L-chain) or L-chain fragment of a clostridial neurotoxin, a targeting domain that binds to a target cell, and a translocating domain that translocates the L-chain or L-chain fragment, however, the effects of the compounds containing various translocating domains and the treating conditions for disease are not sufficiently described in the specification, the invention is highly unpredictable regarding the outcome of the treatment.

(6). Nature of the Invention

The scope of the claims includes a method of treating of hypersecretion of mucus, COPD and asthma using with a compound comprising a light chain (L-chain) or L-chain fragment of a

clostridial neurotoxin, a targeting domain that binds to a target cell, and a translocating domain that translocates the L-chain or L-chain fragment, but the specification has not shown the effect of the compounds comprising various translocating domains. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed methods associated with the variants, and the guidance and the teaching in the specification are limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the outcome of the treatment using the compounds.

Response to Arguments

Applicants indicate the claims are enabled because their scope is commensurate with what is enabled by the specification in light of that which is well known by the skilled artisan. The claims are directed to methods of treating hypersecretion of mucus, chronic obstructive pulmonary disease or asthma using a compound having three components, where the third component, a translocating domain, has the property of translocating the L-chain or L-chain fragment into the target cell, which is readily recognized by the skilled artisan. Moreover, this claim language is fully explained and exemplified in the specification (see paragraphs 0023 to 0025, 0030) such that the skilled artisan would know how to make and use the full scope of the compounds according to the claimed methods without undue experimentation (see paragraphs 0027-0030; Shone et al. (1987) and Blaustein et al. (1987), Exhibits A and B). Applicants also provide four additional references (Exhibits C-F: Lord et al. (1999), Zhang et al. (2004), Haug et al. (2003), and Sandvig et al. (2004)) to indicate several molecules have the desired translocating activity (pages 10-14 of the response).

Applicants' response has been fully considered, however, the argument is not found persuasive because the specification has only demonstrated the in vitro effect of WGA-LH_N/A (Example 3), it has not demonstrated the make/use of compounds containing various translocating domains in treating hypersecretion of mucus, COPD and asthma. Although the specification discloses some known translocating domains (paragraph 0028), and the assays to identify a molecule having translocating domain (paragraph 0030), the specification has not demonstrated the use of the compounds containing various translocating domains in the treatment, it requires undue experimentation to assess their effects in treating hypersecretion of mucus, COPD and asthma. Therefore, the full scope of the claim is not enabled.

Conclusion

5. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Patent Examiner

CHIH-MIN KAM
PATENT EXAMINER

CMK
October 06, 2005